Neurobiological and Clinical Consequences of Stress

From Normal Adaptation to Post-Traumatic Stress Disorder

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Lippincott - Raven
PUBLISHERS
Philadelphia • New York

Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to PTSD, edited by M. J. Friedman, D. S. Charney, and A. Y. Deutch, Lippincott-Raven Publishers, Philadelphia © 1995.

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The Relationship Between Trauma, Post-Traumatic Stress Disorder, and Physical Health

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Since publication of Selye's seminal book, *The Stress of Life* (1), a great deal of research has been aimed at furthering our understanding of the relationship between stress and physical health. Several important reviews have addressed etiological mechanisms through which exposure to stress might affect biological systems that are critical for maintaining health. Chrousos and Gold (2) define a "stress system" that has as its main components the hypothalamic-pituitary-adrenocortical (HPA) system, and the central and peripheral adrenergic system. According to these authors, the stress system can produce a variety of pathophysiologic states that may precipitate vulnerability to or actual expression of a wide range of psychiatric, endocrine, and inflammatory disorders. Specific reviews have focused on literature pertaining to stress-induced impairment of immunologic function (3,4) and increased susceptibility to infectious disease following exposure to stress (5). There also is a relevant literature on the relationship between stress-induced cardiovascular abnormalities and somatic anxiety (6). Kaplan and associates (7) have reviewed studies, many of them their own work, that show how social stress can precipitate atherosclerotic pathology in primates, and Saab and Schneiderman (8) have reviewed laboratory and clinical studies showing a linear correlation between intensity of stress-induced cardiovascular reactivity and later development of hypertension. Kiecolt-Glaser and associates (9) concluded that there appears to be "a convergence among cardiovascular, neuroendocrine and psychoneuroimmunological research and the evaluation of differences among people who vary in autonomic activation. A better understanding of these individual differences in response to stress could help identify those individuals who may be more prone to long-term health changes . . ." (p. 684).

From the perspective of the field of trauma research, it is surprising that so few of the thousands of studies that have been devoted to the topic of stress and physical health have examined the effects associated with extreme stress. As Cohen and Williamson (5) suggest in their review of the literature on stress and infectious disease in humans, "Impact of severe events would provide the fairest test of a stress-disease relationship . . ." (p. 18). Perhaps equally surprising are the examples of severe events offered by Cohen and Williamson: divorce, bereavement, and job loss. While not denying the emotional impact of such events, we believe that an even fairer test of the stress-disease relationship would be provided by the study of extremely traumatic events, including war-zone exposure,

sexual and other criminal victimization, natural and human-made disasters, and serious accidents.

First we review the literature on the physical health outcomes associated with traumatic events. Despite the extensive literature suggesting that exposure to stressful events may be associated with adverse health outcomes, much less has been written on the medical and somatic consequences of exposure to extreme stress. Nonetheless, reviewers have suggested that physical health may be severely and chronically impaired following traumatic experiences such as concentration camp incarceration (10,11), confinement as a prisoner of war (POW) (12–14), war zone exposure during military hostilities (15,16), sexual assault as a child or adult (17–19), or exposure to natural disasters (20). Second, we review the literature on the physical health outcomes associated with post-traumatic stress disorder (PTSD). Like Wolfe and colleagues (21), we argue that PTSD is an important mediator through which trauma may be related to adverse outcomes. Third, we review biological and psychological correlates of PTSD that might predispose affected individuals toward increased risk for medical problems.

METHODOLOGICAL CONSIDERATIONS

Our review includes four categories of health outcome: 1) self-reports; 2) utilization of medical services; 3) morbidity as indicated by physician diagnosis or laboratory tests; and 4) mortality. Self-reports, by far the most commonly measured outcomes, include ratings of health status, symptoms, or illness conditions. There has been much controversy about the validity of self-reports as indicators of an individual's "true" health status, because self-reports may not be confirmed by laboratory tests or diagnostic assessments. For example, male Vietnam theater veterans were found to be more likely than Vietnam era veterans to report poorer health and increased health problems in a variety of domains, yet medical tests failed to corroborate virtually all of the self-reported differences (22,23). We think that it is important to remember that self-reports may not always provide valid information about health or disease, and, specifically, that they may be strongly influenced by psychological states and processes (see further discussion (24,25)). We also think that self-reports should not be dismissed as necessarily or categorically invalid. Self-reports can, at least to some extent, be valid indicators of an individual's physical health status. Self-reported health as rated on a five-point single-item scale is an excellent predictor of mortality (26), and self-reported health indicators can distinguish groups that vary in terms of disease type and severity (27). Accordingly, we have chosen to include self-reports in our review.

Another methodological issue that must be considered when interpreting the literature on stress and physical health is that all of the human studies are correlational, which makes it difficult to infer a causal role for stress or PTSD. As in any correlational problem, it is necessary to specify (i.e., measure and control for) other potential causes. At the same time, it is necessary to interpret the results of most multivariate procedures with extreme caution; we say "most" because we believe that structural modeling offers a more appropriate way to analyze the data in this area. Imagine that an investigator wishes to examine the relationship between amount of exposure to a flood and utilization of medical services in the year following the flood, while controlling for other factors known to influence utilization such as age. The investigator finds that amount of exposure is positively correlated with utilization, but that the relationship is no longer statistically significant when age is taken into account. Should the investigator conclude that amount of exposure has no relationship to utilization? The answer is "no" if age is correlated with exposure because, for example, older individuals tend to live in less sturdy homes that are closer to flood zones. The investigator would make a Type II error by failing to statistically model this relationship in a path or structural model, or failing to pay careful attention to the correlations among independent variables such as exposure and control variables such as age. We provide an actual example of such a complex

relationship in our introduction to the section on PTSD and health that follows.

A further methodological issue is that longitudinal studies are rare, and usually complicated by an absence of pre-exposure or pre-PTSD baseline health data. Baseline information often must be inferred from retrospective self-reports, which may be biased or incomplete. Given this and the aforementioned problems, we believe that it is especially important to examine the literature on trauma, PTSD, and health as a whole, and also to look to the experimental animal literature as reviewed in Part I of this volume.

THE ROLE OF PHYSICAL INJURY

People are sometimes killed, injured, or medically disabled as a direct result of their exposure to traumatic events. Military veterans who survive battlefield wounds may develop permanent medical problems from spinal cord injuries, loss of a limb, and other deficits. Female survivors of rape, criminal victimization, or domestic violence may suffer from acute bodily injury as well as long-term consequences of such damage (19). Ex-POW survivors of prolonged captivity often experience malnutrition, infectious diseases (especially tuberculosis), beatings, torture, prolonged physical exertion (on work details, forced marches, etc.), frostbite, and other stressors. Therefore, it is sometimes difficult, if not impossible, to identify a specific psychological or physical stressor as the major cause of a subsequent medical problem. Furthermore, it is neither useful nor realistic to separate psychological from physical stress in this regard, because each may interact with the other and both undoubtedly contribute to the suffering and despair associated with traumatic exposure.

We readily acknowledge that long-term health consequences may result from injuries or from medical conditions associated with a traumatic event. We do not believe, however, that this alone can account for the many findings (see review that follows) showing that traumatic exposure in general and PTSD in particular are associated with increased risk of adverse health outcomes. Although there is a relationship between severity of injury (28) and risk of PTSD, it is unlikely that injury is the sole cause of the relationship between PTSD and adverse health outcomes. Most people who develop PTSD are not injured as a result of the trauma that caused their PTSD, as illustrated in a study of the discharge summaries of 543 veterans with PTSD. Sixty percent had an identified medical problem and 42% had multiple problems, yet only 8% had physical sequelae of combat-related trauma (29). Also, injury to a specific site or system is unlikely to explain the multiple nature of the physical health complaints and physical morbidity seen in PTSD.

To summarize, it appears that trauma-related injuries and medical problems contribute to subsequent health problems, but their contribution is minor and cannot explain much of the data suggesting that traumatic exposure is associated with adverse health outcomes. Although we will not reiterate this point, it should be kept in mind as a potentially important variable underlying research findings summarized in the following review of the literature.

TRAUMA AND HEALTH

Self-Reports

Most publications in this category concern Vietnam veterans. In a national epidemiological survey, the National Vietnam Veterans Readjustment Study (NVVRS), male and female Vietnam veterans with high war-zone exposure reported poorer health and more health problems relative to era veterans or civilians (15). Other studies have independently shown that combat exposure predicted increased reporting of a variety of health problems among 6,800 male Midwestern Vietnam combat veterans who belonged to the American Legion (16) and among Vietnam combat veterans who believed that they had been exposed to the herbicide Agent Orange, whether or not such exposure had actually occurred (30). Combat exposure also predicted adverse health reports in an elegant study of 2,260 male-male monozygotic twin pairs who partici-

pated in mail or telephone interviews. In comparison with their twins who were not exposed to war-zone stress, the siblings who served in Southeast Asia reported significantly more hearing and skin problems (31). In their Vietnam Experience Study, the Centers for Disease Control (CDC) (22) conducted a telephone survey of 7,924 Vietnam theater veterans and 7,364 Vietnam era veterans. The combat veterans were almost twice as likely to assess their health as "poor" or "fair," and to report a wide variety of medical problems, as the era veterans. However, a further component of the study illustrates how self-reports may not be corroborated by diagnostic tests. A random subsample of 2,490 Vietnam veterans and 1,972 non-Vietnam veterans underwent a comprehensive medical examination that detected few current objective differences in physical health between the two groups (23). Wolfe et al. (21) found a relationship between the magnitude of war-zone exposure and current adverse health reports among female Vietnam veteran nurses, although subsequent analyses suggested that PTSD was an important predictor of the association (see section on PTSD and health that follows).

Many of the publications on adverse health effects among survivors of childhood or adult sexual abuse suggest that women who have a history of sexual victimization are more likely than controls who do not have a history of such exposure to report a variety of medical problems. Female rape victims were more likely to report lower perceived health status, more somatic symptoms, and more negative health behaviors than nonvictim controls (32–34). Somatic symptoms, especially regarding gastrointestinal distress and recurrent headaches (35), as well as dysuria, vaginal discharge, and chronic abdominal pain (36), were reported more frequently by rape or incest survivors than by nonabused controls.

An interesting facet of the sexual trauma and health literature is the suggestion that a history of sexual abuse, especially during childhood, is associated with the presence of chronic pelvic pain (37–39). Walker et al. (40) performed laparoscopic exams on 50 women with chronic pelvic pain and 50 women seeking tubal ligation or infertility evaluation. There was a significant correlation between a history of severe sexual abuse and medically unexplained symptoms; in other words, patients with chronic pelvic pain were more likely than patients in the comparison group to have a positive history of sexual abuse and a normal laparoscopic examination. A different conclusion was reached by Rapkin et al. (41), who found no difference in childhood abuse histories between women with chronic pelvic pain and those with chronic pain in other locations. In fact, childhood physical abuse rather than sexual abuse predicted adult pain syndromes, and was greater for both chronic pain groups than for controls. An important difference between Rapkin et al.'s study and other investigations of chronic pelvic pain is that it was the only study to include a chronic pain (nonpelvic) control group. This may account for the different results reported by these investigators, and underscores the necessity for designing studies with appropriate control groups in order to interpret data pertaining to this complex area.

A review by Hovanitz (20) provides an excellent synthesis of literature on physical health outcomes associated with the aftermath of disasters. Most of the studies reviewed concern the aftermath of floods, and Hovanitz concludes that, in all of these studies, severity of exposure to flood trauma was associated with increased reports of health problems. Two studies of individuals who had been assessed before exposure to the severe Puerto Rican flood of 1985 and were reinterviewed in 1987 indicate a small but significant increase in somatic symptoms (42, 43). Similarly, among older adults exposed to the 1984 flood in southeastern Kentucky who were interviewed 18 months afterwards, severity of flood exposure was related to reported magnitude of somatic symptoms (44).

Two self-report studies concern survivors of a volcanic eruption. Murphy (45) failed to find a relationship between severity of trauma and physical health reports among survivors of the 1980 Mount Saint Helens eruption, although she looked only at change from 11 months after the eruption to 35 months after. Among survivors of the 1987 volcano that destroyed Armero, Colombia, those who reported emotional dis-

tress 7 months after the disaster were more likely than those who were not distressed to report nonspecific physical problems and to have multiple physical complaints (46).

Uba and Chung (47) found that, among Cambodian refugees living in the United States, the amount of traumatic exposure during the war in Cambodia was positively related to poor health outcomes more than 10 years later. Mollica et al. (11) found that therapeutic intervention actually worsened somatic symptoms but improved psychological symptoms among Cambodian, Hmong, Laotian, and Vietnamese refugees previously exposed to the war in Southeast Asia. Van der Ploeg and Kleijn (48) compared Dutch men and women previously held hostage during terrorist hijackings with family members not abducted. Six to 9 years after captivity, the ex-hostages reported significantly higher rates of migraine or severe headache, intestinal problems, rheumatic problems and pains, skin diseases (eczema), and stomach problems. Bartone et al. (49) interviewed military family assistance officers 6 months and 1 year after a U.S. Army airplane crash in Gander, Newfoundland, in 1985 that killed 248 soldiers. Results showed a robust dose-response relationship between severity of exposure to survivor stress (the intensity and duration of contact with surviving family members) and magnitude of self-reported physical symptoms or illnesses. Two studies concern the relationship between exposure to motor vehicle accidents and the subsequent development of chronic pain and PTSD (50,51).

Utilization

The National Academy of Sciences follow-up of 2,500 U.S. Army World War II and Korean conflict ex-POWs has generated an important dataset regarding utilization of medical resources following the extreme stress of POW captivity (12,13). The most notable increases in hospital admission rates for POWs versus controls were for psychiatric disorders, nutritional problems, tuberculosis, and other infectious and parasitic diseases. In addition, POWs had higher hospitalization rates for cardiovascular and gastrointestinal diseases in contrast to non-POW veteran controls. Similar results were found by Eitinger (10) in his morbidity studies of Norwegian survivors of Nazi concentration camps. Survivors had more sick periods, longer sick leaves, and more frequent and longer-lasting hospitalization periods than controls.

A number of studies have shown increased utilization of medical resources among women with histories of recent or lifetime sexual assault, physical assault, or criminal victimization. Kimerling and Calhoun (32) prospectively compared utilization rates among women who had been recently raped with a matched control group for 1 year after the victims' assault. By 4 months post assault, the victim group reported increased medical (but not psychological) service utilization that persisted at the 1-year follow-up. Waigandt et al. (34) also found that sexual assault victims reported significantly more doctor visits for a prolonged period (2 years) after the rape than a matched control group.

Koss et al. (33) found twice as many physician visits (and 2.5 times greater medical expenses) among women who had been exposed to criminal victimization in comparison with controls, during the first year following the assault. Severity of victimization was the most powerful predictor of physician visits and outpatient costs. Similarly, Norris et al. (52) interviewed men and women exposed to violent crime 6 and 12 months after the assault and compared them with adults who had been subjected to property crimes but who had not been physically attacked. Medical (as well as mental health, legal, and pastoral) utilization rates were significantly elevated among the physically victimized cohort in contrast to victims of property crimes. In a study of Swedish battered women, Bergman and Brismar (53) examined medical records for 10 years preceding and 5 years after the battering, and compared them with records of a matched control group. In addition to hospital admissions for injuries directly related to the battering, battered women had significantly increased admission rates for nontraumatic surgical disorders, gynecological disorders, induced abortion, medical disorders, suicide attempts, and inpatient observation.

With regard to female adult survivors of childhood or adult sexual abuse seeking treatment at an outpatient clinic for gastrointestinal disorders, Drossman et al. (37) found that victimized women reported more lifetime surgeries than nonabused controls, although there was no difference in number of physician visits per 6 months or number of hospitalizations per 2 years. Finally, Felitti (35), reviewing utilization patterns among lifetime sexually abused patients receiving treatment at an HMO, found that they were more likely than a nonabused comparison group to exhibit a high utilization pattern (10 or more doctor office visits per year).

Increased medical utilization also has been observed following natural disasters. Hospital referrals more than doubled following the Bristol, England, flood in 1968. There was no relationship between flood-related injuries and referral rates, but a clear dose-response relationship between depth of flooding and medical utilization was found (54). A similar increase in visits to health-care practitioners, especially among males, was reported following the 1974 flood in Brisbane, Australia (55). During the 7 months following the 1980 eruption of Mount Saint Helens and subsequent ashfall, there was a significant increase, relative to the 7 months prior to the eruption, in emergency room visits but not in hospital admission or occupancy rates (56).

Morbidity

The largest body of information in which adverse health outcomes are documented by a medical examination concerns the aftermath of war trauma. Although most of the studies focus on military veterans, including POWs, there are important publications on the medical status of civilians exposed to concentration camp and/or war-zone trauma.

Longitudinal studies of World War II and Korean POWs have been conducted in Canada, Australia, and the U.S. A number of reports have appeared on a National Academy of Sciences follow-up of over 2,500 U.S. Army repatriated POWs following World War II and the Korean War who were compared with approximately 2,500 U.S. Army non-POW veteran controls. In general, POWs had higher rates of medical illness in most organ systems, but interpretation is difficult, as noted previously. The POWs also had greater psychiatric morbidity than non-POW controls (12,13,57). Goulston et al. (58) assessed gastrointestinal symptoms among a random sample of surviving Australian World War II POWs and non-POW veteran controls 40 years after the stress of internment. Duodenal ulcers and strongyloidiasis were more prevalent in the POW group. Venn and Guest (14) reviewed studies of former Australian POWs and found five conditions consistently associated with imprisonment: 1) strongyloidiasis; 2) peptic ulcer; 3) anxiety states; 4) depression; and 5) hepatitis B. Among Canadian POWs, higher prevalence rates of gastrointestinal, neurological, and cardiovascular disease were found in comparison with non-POW controls (59). A second Canadian study found no difference in rates of heart disease between POWs and non-POW siblings, although POWs had higher cardiovascular morbidity than expected for the Canadian male population (60).

Eitinger's (10) classic mortality and morbidity study of 498 Norwegian World War II concentration camp survivors and matched controls has the same interpretive problems as the POW studies because of the terrible physical and hygienic conditions in the camps. Ex-prisoners had higher rates of tuberculosis, cardiovascular and respiratory disease, and both gastric and duodenal ulcers.

The CDC (23) Vietnam Experience Study mentioned earlier, in which subjects received comprehensive medical exams, detected few differences in physical health between Vietnam war-zone victims and Vietnam era veterans. The exceptions were hearing loss and decreased sperm count among war-zone veterans. These findings, which differ markedly from the investigators' self-report data (22), suggest that there may not be a relationship between traumatic exposure and the development of medical problems. However, veterans enrolled in the CDC study were approximately 37 years old at the time that they were examined. This may be too early for a stress-induced vulnerability to pro-

duce a detectable medical abnormality. We hope that the CDC will carry out a follow-up evaluation when these veterans are in their 50s.

Perhaps the most interesting reports in this group of studies concern coronary heart disease among civilians exposed to war-zone stress. Sibai et al. (61) studied patients who underwent coronary angiography at the American University of Beirut Medical Center during the Lebanon Civil War. Exposure to acute and chronic war stress was higher in patients with abnormal coronary angiographies than in patients with normal angiographic findings. A similar report documented a higher incidence of acute myocardial infarction during the civil war in Croatia than during the same time period during the previous year before the outbreak of hostilities (62).

Two reviews of literature on morbidity following sexual trauma (17,63) emphasize that, since most of the few studies in this area lack methodological rigor, it is difficult to link medical illnesses to childhood sexual abuse. Each reviewer, however, comes to a different conclusion. On the one hand, Laws (63) states that a history of sexual abuse is common in women with a history of chronic pain (especially pelvic pain), functional bowel disorders, eating disorders, obesity, and alcohol abuse. On the other hand, Fry (17) concludes that the findings from more recent studies have called into question results from some of the earlier reports suggesting links between childhood sexual abuse and specific physical symptoms.

Among consecutive admissions to an interdisciplinary inpatient pain rehabilitation program, Wurtele et al. (64) observed that 39% of women and 7% of men reported childhood sexual abuse. Felitti (35) found that sexually abused patients seen in general practice were more likely than controls to have morbid obesity. Drossman et al. (37) observed that 89% of consecutive patients admitted to a GI clinic reported childhood or adult sexual abuse. Patients with a functional disease (irritable bowel syndrome, nonulcer dyspepsia, chronic abdominal pain, constipation, etc.) were more likely than those with organic disease (Crohn's disease, ulcerative colitis, acid peptic disease, liver diseases, etc.) to report a history of forced intercourse or frequent physical abuse.

Two weeks after the 1980 earthquake in southern Italy, subjects exhibited elevations in heart rate, serum cholesterol, and triglyceride levels. These increases were no longer present 7 years later (65). Eight years after a North Sea oil rig disaster that occurred in 1980, Norwegian survivors exhibited significant increases in "psychosomatic diagnoses" such as cardiovascular disease (mostly hypertension), musculoskeletal problems, lower back pain, and dermatological problems in comparison to control subjects (66). Increased morbidity was found among survivors of the floods in both Bristol, England, in 1968 and Brisbane, Australia, in 1974 (54,55). Higher rates of leukemia, lymphoma, and spontaneous abortion were observed after the flooding in western New York that followed Hurricane Agnes in 1972 (67). Adams and Adams (56), who used archival data to study a community before and after the eruption of Mount Saint Helens, reported a greater number of stress-aggravated and psychosomatic illnesses, as well as increased employee sick leave. Murphy (45) failed to find effects due to amount of trauma among survivors who were studied 11 and 35 months after the eruption. As noted by Hovanitz (20), there are enough methodological differences between the last two studies to make direct comparison difficult.

Mortality

Several reports concerning American World War II and Korean War ex-POWs have reported excess mortality in comparison to non-POW controls due mostly to accidental trauma, tuberculosis, suicide, and cirrhosis of the liver. Highest mortality rates occurred during the years immediately following repatriation and converged to control rates by the 9th to 13th year. Other causes of death cited in some, but not all, follow-up studies include atherosclerotic cardiovascular disease, hypertension, and GI problems (12,13, 57,68,69). Similar results were found regarding Australian World War II former POWs who had significantly elevated death rates from liver cir-

rhosis, tuberculosis, arteriosclerosis and degenerative heart disease, motor vehicle accidents, and suicide (70). Accidents and suicide tended to occur within the first 5 years after imprisonment, whereas other causes of death remained elevated up to 18 years after repatriation. Perhaps the best-documented evidence of an association between war-related trauma and mortality from acute myocardial infarction is the report on Croatian civilians exposed to the recent civil war in that country (62).

In a study by the CDC, Vietnam theater veterans also exhibited increased mortality due to motor vehicle accidents, suicide, homicide, and accidental poisoning during the first 5 years postdischarge (71). It is noteworthy that death due to circulatory disease was significantly lower among Vietnam theater veterans than among era veteran controls. In a comparison of drafted Vietnam theater veterans versus not-drafted draft-eligible men, Hearst et al. (72) also found higher mortality rates due to suicide, motor vehicle accidents, and all causes of death. The final study on Vietnam veterans concerns women, mostly nurses, who served in the war zone. Thomas et al. (73) found an increased mortality due to uterine and pancreatic cancer among the war zone veterans in contrast to era veteran controls; as in the CDC's study of male veterans (71), there was lower mortality due to circulatory disease in the theater veterans.

Following the Newcastle earthquake in New South Wales, Australia, there was a significant increase in fatal myocardial infarctions and coronary deaths among people aged less than 70 years. This increase in fatal cardiac deaths lasted for the 4 days immediately after the earthquake and returned to normal levels during the next 4 months (74). For the first 12 months following the Bristol, England, flood in 1968 there was a 50% increase in deaths compared to the previous year (54). In contrast, there was no increased mortality following the Brisbane, Australia, flood in 1974 (55). Increased mortality rates, especially due to malignancies and spontaneous abortions, occurred in western New York following the flooding of the river valley by Hurricane Agnes in 1972 (67). Based on obituaries in a local paper, Adams and Adams (56) reported a substantial increase in the death rate (during the 7 months following, in contrast to the 7 months preceding the disaster) in a community that was traumatized by the Mount Saint Helens eruption and ashfall.

Summary

The trauma and health literature is impressive for the consistency of results showing that exposure to catastrophic stress is associated with adverse health reports, medical utilization, morbidity, and mortality among survivors (see Table 1).

The trauma and health literature also is a large, uneven, and often methodologically flawed body of work. Readers who are skeptical about whether trauma has any "real" effects on physical health can find plenty of support for their position. As indicated in Table 1, the self-report and utilization data are more extensive and conclusive than studies on morbidity or mortality. Also, the self-report findings of one large study did not correlate with physical exam and laboratory findings (22,23). Moreover, as previously stated, morbidity data concerning survivors of long-term imprisonment need to be interpreted cautiously, because the many privations endured during such captivity increased the risk of adverse health outcomes above and beyond the possible independent contributions of PTSD.

To address these kinds of concerns, we again must emphasize the general consistency of findings across diverse trauma populations and outcomes and, in particular, the fact that the self-report and utilization data are supported by the

TABLE 1. *Summary of results concerning the relationship between traumatic exposure and adverse health outcomes*

	Outcome			
Trauma	Self-report	Utilization	Morbidity	Mortality
Military	++	+	+/−	+
Sexual	++	++	+/−	NA
Disaster	+	+	+	+/−
Other[a]	++	NA	+	+

[a]Includes war refugees, hostages, and motor vehicle accident survivors.

++, clear association; +, probable association; +/−, inconsistent information; NA, information not available.

morbidity and mortality data. For example, studies showing a greater occurrence of atherosclerotic heart disease among Lebanese (61) and Croatian (62) civilians during civil war are quite persuasive, as are documented increases in mortality due to cardiovascular events among civilians during wartime (62) and following natural disasters (54,74). Interpreting the self-report and utilization literature in light of such findings brings up the question of parsimony; we believe that a true effect of trauma on physical health is the best single explanation that could underlie all of the data.

PTSD AND HEALTH

PTSD as a Mediator of the Relationship between Trauma and Physical Health

The foregoing section documents evidence of poor health outcomes in individuals who have experienced an extremely traumatic event. A question that has been largely unaddressed in this literature is the role of PTSD in the relationship between trauma and health. Cohen and Williamson (5) discuss the distinction between stress (i.e., a stressor) and distress (the reaction to a stressor) in their review of the literature on stress and infectious disease. We believe that a similar event-reaction distinction is in order when considering traumatic events and, further, that PTSD is a major mediator of the relationship between trauma and health. The reasoning behind our position is illustrated in the following example. Wolfe et al. (21) used multiple regression to examine the effects of war-zone exposure and PTSD on self-reported health outcomes in 109 female Vietnam veterans, first by examining each variable separately and then by examining the effects of each variable while controlling for the other. They found robust effects of both variables on all of the health outcomes that they studied when each variable was considered separately, but when both exposure and PTSD were simultaneously included in the models (all of which included age, education, and health before Vietnam as covariates), only PTSD robustly predicted poor health outcomes. In other words, the association between war-zone exposure and poor health was dramatically reduced when PTSD was taken into account.

This marked decrease in the effects attributable to war-zone exposure after adjusting for PTSD suggests an important mediational role for PTSD in the association between exposure and perceived health. We tested this hypothesis by performing path analyses to predict two of Wolfe's primary outcomes, self-reported current health and number of current health problems. As in Wolfe et al.'s multiple regression analyses, war-zone exposure and PTSD served as predictors, and age, education, and health before Vietnam were included as covariates. In each model, we tested the direct effects of all variables on each outcome and the indirect effects of exposure, age, education, and health before Vietnam as mediated by PTSD; only the results for PTSD and exposure are reported here. (Full details of the analyses are available from the second author.) An advantage of this approach is that it allowed us to determine how much of the relationship between trauma and health is direct, as opposed to predicted by the association between trauma and PTSD.

We found that war-zone exposure had statistically significant total effects on both current health and number of problems (standardized path coefficients of .511 and .432, respectively, $ps < .001$). For current health, 56% of the total effect was indirectly mediated through PTSD (standardized path coefficient = $-.295$, $P < .001$), although there also was a direct effect of exposure (standardized path coefficient = $-.216$, $P < .01$). For number of current health problems, only the indirect effect of exposure, 76% of the total, was statistically significant (standardized path coefficient = .326, $P < .001$). These analyses illustrate the importance of PTSD—the reaction to a trauma—in mediating the relationship between trauma and physical health.

Self-Reports

Several studies have found that PTSD is associated with complaints of poor health outcomes in military veterans (15,75,76) and active duty personnel (76). This association does not seem to

be either gender- or nationality-specific. Similar findings have been reported for Israeli (77,78), New Zealander (79), and Canadian male veterans (80), as well as for female veterans (15,21, 76). The health problems associated with PTSD include multiple physical symptoms and systems. For example, Wolfe et al. (21) found that PTSD (controlling for amount of war-zone exposure) was associated with increased likelihood of cardiovascular, gastrointestinal, gynecological, dermatological, opthamological/otolaryngological, and pain problems. Shalev et al. (77) found that combat veterans with PTSD were more likely than combat controls to report cardiovascular, neurological, gastrointestinal, audiological, headache, and back pain problems. Litz et al. (75) examined self-reports of symptoms and physician-diagnosed disorders, and found that PTSD was associated with elevations for 17 of the 22 symptoms studied, although not with more physician-diagnosed disorders. In contrast, Long et al. (79) found that PTSD was associated with increased numbers of both symptoms and chronic disorder.

To our knowledge, there is only one study of the relationship between PTSD and health complaints among non-veterans. Breslau and Davis (81) found that young community-residing adults whose PTSD lasted at least 1 year reported more medical conditions than those whose PTSD lasted less than a year.

Utilization

It would be reasonable to expect that PTSD is associated with increased use of medical services, given that complaints of poor health are increased in PTSD. The NVVRS found that Vietnam veterans with PTSD reported increased use of medical health services (15); similar findings were reported by Long et al. (79) for New Zealand Vietnam veterans. Long et al. (79), as well as Card (82), found that PTSD was associated with increased disability days due to illness, which suggests that the problems experienced by individuals with PTSD may affect occupational and social function. One study suggests that the relationship between PTSD and utilization of medical services may be additionally influenced by other factors. Garfein et al. (83) examined the likelihood of receiving VA inpatient treatment for cardiovascular, cerebrovascular, and gastrointestinal problems among patients who had either PTSD, major depressive disorder, or schizophrenia. The hyperarousal and hyperreactivity in PTSD could be argued to make these disorders more likely among the PTSD group (75). The PTSD group was more likely than the schizophrenic group to have used inpatient services for cardiovascular or gastrointestinal problems, but did not differ from the depressed group. This finding highlights the need for psychiatric controls, especially those that share overlapping symptoms with PTSD patients (such as depression and alcohol abuse), to be included in studies of the relationship between PTSD and physical health outcomes.

Morbidity and Mortality

Only a few investigators have examined the relationship between PTSD and morbidity, and no one has examined mortality. Yet, as just noted (29), 60% of a sample of PTSD inpatients in a VA hospital were found to have an identified medical problem, and 42% had multiple problems. Lipton and Schaffer (84) reported multiple, severe medical problems among patients receiving psychotherapy in a PTSD treatment program.

We have found three studies that report cardiovascular morbidity information for individuals with and without PTSD, and all show increased morbidity associated with PTSD. Falger et al. (85) compared veterans of the Dutch Resistance in World War II who currently had PTSD with men of comparable age who had recently had either surgery or a myocardial infarction (MI). The PTSD group was comparable to the MI group in prevalence of angina (31% versus 26%, respectively), and higher than the surgery group (7%). Litz et al. (86) studied male Vietnam combat veterans and found that PTSD predicted poorer effort tolerance in a laboratory stress test.

Similar results were reported by Shalev et al. (77) for Israeli combat veterans with PTSD who did not differ from non-PTSD controls on physical exam and laboratory test findings. Although the PTSD veterans were more likely to smoke, Shalev et al. observed a difference in effort tolerance even when PTSD and no PTSD groups were stratified based on smoking status (yes/no); in other words, effort tolerance was poorer in veterans who had PTSD regardless of whether they smoked.

Whereas Litz et al. (86) found no association between PTSD symptoms and total cholesterol, Zimering et al. (87) have recently reported that male Vietnam veterans with PTSD have unfavorable blood lipid profiles, relative to combat veterans without PTSD. The groups in Zimering et al.'s study were equivalent in terms of hypertension and family history of heart disease, and smoking was controlled, so the effects cannot be attributed to these risk factors for cardiovascular disease. Still, as we are about to discuss, PTSD is associated with poor health habits (77,86). Therefore, other risk factors may have contributed to the difference between groups.

Summary

PTSD is associated with increased complaints of poor health, utilization of medical services, and cardiovascular morbidity. Caution is warranted when interpreting the data because there are relatively few studies in the area, and only one of the cardiovascular morbidity studies used controls who had a major psychiatric disorder other than depression (83). Despite the similarity observed in that study between PTSD and major depressive disorder (in utilization of inpatient medical services), we believe that PTSD is distinctive among psychiatric disorders in terms of its potential to promote poor health. As a reaction to extreme trauma, PTSD is an important mediator of the relationship between trauma and health. Next we discuss this mediational role in light of known biological, psychophysiological, and psychological components of PTSD.

FACTORS THAT MAY EXPLAIN THE RELATIONSHIP BETWEEN PTSD AND HEALTH OUTCOMES

Neurobiological Factors

Rosen and Fields (88) were the first to propose that neurochemical changes in the brain associated with PTSD might be etiologically related to the long-term morbidity observed in trauma victims. They focused specifically on the cardiovascular and gastrointestinal disorders observed in World War II POWs (12,13), which they hypothesized had resulted from PTSD-related alterations in brain catecholaminergic activity. Friedman (89) expanded this conceptual approach, and cited literature dating back to 1864 that presumes a relationship between combat trauma and cardiovascular illness. He speculated that the pathophysiology of PTSD might be etiologically responsible for cardiovascular abnormalities observed among war veterans who have received a number of diagnostic labels, including soldier's heart, Da Costa's Syndrome, and neurocirculatory asthenia.

As emphasized throughout this book, many of the biological systems affected by exposure of animals to stressful laboratory paradigms exhibit stable alterations in humans with PTSD. The best documented abnormalities associated with PTSD include enhanced cardiovascular reactivity, autonomic hyperarousal, disturbed sleep physiology, adrenergic dysregulation, enhanced thyroid function, and altered HPA activity. Taken together, these findings suggest that the pathophysiology of PTSD is such as to increase the risk for a number of medical illnesses. Specifically, it appears that excessive sympathetic reactivity and adrenergic dysregulation will increase vulnerability to cardiovascular disorders such as hypertension (8) and atherosclerotic heart disease (7). Endocrinological abnormalities such as HPA dysregulation, altered thyroid function, and possible alteration in testosterone and growth hormone (see Chapters 13, 18, 20, and 24) might increase vulnerability to specific endocrinopathies. In addition, such abnormalities, especially in the HPA system, may increase susceptibility to infections and immunologic disorders. Opioid

dysregulation would certainly be expected to affect pain perception, pain tolerance, and chronic pain syndromes (90), as well as to impair endogenous cardiovascular regulation (91).

If certain abnormalities shown on animal stress paradigms are also found in humans with PTSD, we predict that there will be increased risk for medical illness among these patients. In particular, we predict that immunologic abnormalities will be shown to be reliably associated with PTSD. We base this prediction on psychoimmunologic research findings (see Chapter 21), on the stress and health literature (3,5), and on known interactions between immunologic function, the HPA axis, and the central and peripheral adrenergic systems (2,92). Finally, in addition to affecting susceptibility to infectious disease, a dysregulated immune system might also increase the risk for autoimmune disorders among PTSD patients. We predict that additional disease vulnerabilities will be identified among PTSD patients after other laboratory stress-induced abnormalities are found in human patients. These include alterations in corticotropin-releasing hormone (CRH), peptidergic, serotonergic, cholinergic, gamma-aminobutyric acid (GABA)-benzodiazepine, and dopaminergic systems.

Elsewhere in this volume, Post and colleagues discuss the applicability of sensitization models such as kindling and behavioral sensitization to PTSD. It is possible that a sensitization mechanism might cause individuals with PTSD to be at increased risk for medical disorders, for which a limbic sensitization model has been proposed (e.g., multiple chemical sensitivity syndrome (MCS) (93)). This latter speculation (for which the authors accept full responsibility) may be pertinent to preliminary data suggesting that American veterans of the Persian Gulf War who have PTSD may be at greater risk than colleagues without PTSD for symptoms suggestive of MCS.

To summarize, there appears to be good agreement between adverse health outcomes that one would predict based on our emerging understanding of the pathophysiology of PTSD and adverse health outcomes that have been reported in the literature concerning patients with PTSD.

Psychological and Behavioral Factors

A number of psychological and behavioral correlates of PTSD are themselves known risk factors for negative health outcomes. These correlates, and their relationship to PTSD, are so interrelated as to make separate discussion of each one virtually impossible. They may operate directly by creating psychological states that are potentially unhealthy (e.g., hyperreactivity), and indirectly by increasing the likelihood of unhealthy habits.

The literature reviewed by Williams (see Chapter 22) shows that hostility predicts poor cardiovascular health. Hostility and anger are increased in PTSD (94,95); thus, individuals who have PTSD could be at risk for cardiovascular disease. This risk could be related to the same mechanism by which trauma-related hyperreactivity is postulated to operate (7,8). Additionally, the risk could be related to poor health behaviors. Siegler et al. (96) found that hostility measured in college students predicted increased adult risk factors for coronary artery disease (including caffeine intake, body mass index, unfavorable lipid ratios, and smoking). In the same study, adult hostility was associated with increased risk on all of these factors plus alcohol consumption and hypertension. Individuals with PTSD have increased health risk assessment scores (86) and are more likely to smoke (77,87) and have alcohol problems (15). In fact, one longitudinal study of Israeli combat veterans found that increases in PTSD were associated with increases in alcohol consumption and smoking (97). Smith (98) discusses increased interpersonal stress—low social support and high conflict—as another explanation for the relationship between hostility and health. Poor social support has been found in several studies to be related to PTSD (99).

Health outcomes associated with depression also may be responsible for any association between PTSD and physical health. Depression is a common comorbid diagnosis among individuals with PTSD (15). Depressed individuals report more physical symptoms and use more medical treatment than nondepressed individuals (see review (100)). One possibility is that physical

symptom inventories often include symptoms that are components of anxious and depressed states, such as headaches, nausea, and breathlessness. This is a plausible, although only partial, explanation for Litz et al.'s (75) observation of increased symptom complaints in combat-related PTSD. Another possibility is that depressed individuals are simply presenting their psychological distress in a somatic context (100). The relationship between depression and health outcomes is not only observed for self-reports and utilization, however; like hostility, depression has been linked to increased mortality in cardiac patients (101) and to poorer immune function (102). Moreover, depression interferes with good health habits (103). For example, depression is associated with reduced success at quitting smoking (104,105) and with increased alcohol consumption (106).

Like depression, alcohol and substance abuse are common comorbid diagnoses in PTSD (15,107). Both are significant public health problems. Although smoking is related to excessive drinking (106,108), heavy drinking is associated with increased cardiovascular morbidity and mortality when smoking is taken into account (108,109).

Our discussion would be incomplete if we did not include coping as a potential mediator of the relationship between PTSD and physical health. As noted by Aldwin (110), a major reason for studying coping is that coping is thought to moderate the negative effects of stress on health. Although much remains to be learned about coping in PTSD, it appears that PTSD is related to avoidant and emotion-focused coping (111–113), strategies that often are associated with psychological distress and physical symptoms (but see evidence that the efficacy of a particular strategy may depend on the perceived controllability of a stressor (114)). Aldwin mentions direct, mediational, and moderating (buffering) pathways by which coping could influence physical health. To our knowledge, only one study has included PTSD in tests of these pathways (115). The authors used a longitudinal design and hierarchical multiple regression to predict time 2 somatic symptoms as a function of variables that were significantly correlated with these symptoms: time 1 somatic symptoms, time 2 PTSD, negative life events, coping, and social resources. After controlling for initial symptom levels, only PTSD and social resources predicted symptoms at time 2; interactions involving coping, which would have provided tests of moderating pathways, were not statistically significant. Still, we suspect that the mediating and moderating roles of coping are likely to be important in understanding the relationship between PTSD and physical health. For example, if one adopts avoidant strategies such as alcoholism and substance abuse in order to cope with intrusive symptoms, the effects of avoidant coping are actually being mediated by these behaviors.

CONCLUDING COMMENTS

A number of authors have reviewed the relationship between health and sexual trauma (17–19,63), natural disasters (20), and POW captivity (13). There also have been large-scale studies on the adverse health consequences of military trauma, including war-zone exposure (15,16), POW captivity (12–14), and civilian incarceration in a concentration camp (10). This review, to our knowledge, is the most comprehensive effort at identifying and synthesizing the entire English language literature on trauma and health, and at extending the focus to question the relationship between PTSD and health.

We have taken as our starting point the massive stress and health literature, which, beginning with Selye's classic work (1), has shown that exposure to laboratory stress, everyday hassles, and severe events such as divorce, bereavement, and job loss can produce physiological abnormalities, impaired immunologic function, and increased susceptibility to infection (2–5, 7–9). We agree with Cohen and Williamson (5), who suggested that a review of the impact of traumatic events on health would be the "fairest test of the stress-disease relationship" (p. 18), and believe that the literature strongly suggests a clear association between exposure to extreme stress and poor health.

Following the suggestions of Rosen and Fields (88), and Friedman (89) that the adverse health consequences of POW and military trauma are due substantially to PTSD, we have reviewed the PTSD and health literature in its entirety. This is a much smaller body of work than either the stress and health or even the trauma and health literature, but it too supports this conclusion. Most of the existing studies are based on self-reports of physical health, and to a lesser extent on utilization, but the few studies of morbidity also found PTSD to be related to poor health outcomes.

When viewing the literature on trauma, PTSD, and physical health, it is important to recognize the general consistency of findings across self-reports and more objective outcome domains. The consistency bolsters our interpretation of the self-report data as a valid indicator of health status. We raise this issue because of a concern in the everyday stress literature that self-reported physical symptoms substantially reflect neuroticism, or "negative affectivity" (NA) (116). NA is associated with increased self-reports of physical symptoms, presumably because individuals high in NA experience exaggerated perception of and reaction to mild physical symptoms. One significant characteristic of NA is that it is related to self-reported symptoms, but not to utilization, morbidity, mortality, or disease risk factors (116). This pattern of relationships stands in marked contrast to patterns observed for trauma and PTSD. Thus, although NA may partially be the mechanism whereby trauma and PTSD are related to self-reported symptoms, it is unlikely to be the primary mechanism. Furthermore, it is even less likely that NA is the primary mechanism relating trauma and PTSD to other health outcomes.

We believe that PTSD is distinctive among psychiatric disorders in terms of its potential to promote poor health because of both the physiological and psychological abnormalities associated with this disorder. Specifically, it appears that medical problems may result from demonstrated biological alterations such as sympathetic hyperreactivity, adrenergic dysregulation, endocrinological abnormalities, opioid dysregulations, and probably (we speculate from the stress and health literature) altered immunologic mechanisms. Of equal importance, psychological and behavioral abnormalities associated with PTSD are likely to promote poor health. These include hostility, depression, poor health habits (smoking, drinking, drug use, and abnormal eating behavior), and poor coping skills. We believe that there are crucial cumulative and interaction effects between each of these biological and psychological factors through which PTSD promotes poor health.

There are several implications of this conclusion. From a scientific perspective, future research on stress and physical health should pay much more attention to the physical health outcomes associated with extreme stress and PTSD. Furthermore, PTSD investigators should pay more attention to the medical consequences of PTSD. In both cases, researchers should attempt to include multiple physical health outcome domains whenever possible. From a clinical perspective, medical practitioners should take a careful trauma history in their overall assessment of patients. Mental health practitioners should monitor medical complaints and consider the possibility that their patients' physical health status may be related to PTSD. Finally, the strictest test of this proposed relationship between PTSD and poor health would be to provide PTSD treatment to PTSD patients with medical problems. Controlling for equal medical interventions, we speculate that patients whose PTSD responds favorably to treatment might benefit medically. Such benefits might take several forms. In the case of early intervention, successful PTSD treatment might promote improvement in physical health. In the case of chronic PTSD and long-term medical problems, PTSD treatment might slow or halt the progression of well-established disorders.

Powerful institutional and conceptual factors interfere with the medical/mental health collaboration that we deem essential for diagnosis and treatment of PTSD-related medical problems. The major institutional factor is the segregation of clinicians into medical, surgical, and mental health divisions. The major conceptual factor, which we consider more powerful and insidious, is a pervasive eighteenth-century mind-body du-

alism that remains influential in many medical circles.

Our assertion that PTSD promotes poor health through a complex interaction between biological and psychological mechanisms flies in the face of such dualism. We hope that the present literature review and discussion will help to foster the crucial medical/mental health collaborative initiatives needed to address the problem of trauma-related medical illness, and lead to better diagnosis and treatment of such disorders in the future.

ACKNOWLEDGMENTS

We would like to thank Drs. Carolyn Aldwin and Ilene Siegler for their helpful comments on an earlier version of the manuscript.

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